IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE HONORABLE BOARD OF PATENT APPEALS AND INTERFERENCES

In re PATENT APPLICATION OF

Robert B. DICKSON *et al.*

Application No. 09/936,333

Filed: March 5, 2002

Examiner: Zachariah Lucas

Group Art Unit: 1648

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BRIEF ON APPEAL

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I. INTRODUCTION

This appeal is from an official action mailed August 10, 2005, finally rejecting claims 15, 16, 18, 19, and 34-36 of the above-identified patent application.

A. Real Party in Interest

The real party in interest for this appeal and the present application is the Georgetown University School of Medicine, by way of an Assignment recorded in the U.S. Patent and Trademark Office at Reel 012770, Frame 0529.

B. Statement of Related Appeals and Interferences

There are presently no appeals or interferences known to Appellants, the Appellants' representatives or the Assignee, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

C. Status of Claims

Claims 15, 16, 18, 19, and 34-36 are pending. Claims 15 and 19 are allowed, and claims 16, 18, and 34-36 stand rejected and are on appeal. The claims on appeal are set forth in the attached Appendix A. Claim 16 is independent, and claims 18, and 34-36 depend from claim 16.

D. Status of Amendments Filed Subsequent to Final Rejection

An amendment under 37 C.F.R. §1.116 was filed November 8, 2005, in response to the final official action mailed on August 10, 2005. The advisory action mailed November 30, 2005, indicated that for purposes of appeal, the amendment filed November 8, 2005, would be entered of record, and that claims 15 and 19 would be allowed, and claims 16, 18, and 34-36 would remain rejected.

II. SUMMARY OF THE CLAIMED INVENTION

A. Overview

The applicants have discovered that human matriptase, a serine protease enzyme associated with tumor growth and invasion, is converted from an inactive single-chain form (zymogen) to a proteolytically active, two-chain form, by cleavage at a specific site within the matriptase polypeptide. Prior to the applicants' discovery, the active, 2-chain form of matriptase

had not been isolated, described or characterized. The applicants have characterized the active, two-chain form of the enzyme by describing its amino acid sequence and the location of the site of cleavage that activates the enzyme, and by demonstrating that Hepatocyte Growth Factor Activator Inhibitor-1 (HAI-1) binds to the two-chain form of matriptase and inhibits the active protease, but does not bind to the inactive, single-chain form. The applicants have further demonstrated the production and identification of hybridomas that make monoclonal antibodies that specifically recognize and bind to the active two-chain form of human matriptase as their antigen, and have negligible affinity for the single-chain form of matriptase. Prior to the applicants' discovery, it was not known that matriptase is produced by human cells as an inactive single-chain polypeptide that is cleaved to form a proteolytically active two-chain form of matriptase, nor was it known that monoclonal antibodies could be prepared and identified that are capable of binding specifically to the two-chain form of matriptase as their antigen, and have negligible affinity for the inactive, single-chain form of matriptase.

B. Object of the Invention

It is an object of the invention to provide antibodies that bind specifically to the two-chain form of human matriptase and have little or no affinity for the single-chain form of matriptase.

C. Embodiment of the Invention

The application describes a method for preparing monoclonal antibodies that are capable of binding to the two-chain form of human matriptase as their antigen, *i.e.*, they bind specifically to the active, two-chain form of human matriptase and have little or no affinity for the inactive, single-chain form of human matriptase. The application describes (a) preparing hybridomas that produce monoclonal antibodies that bind to the two-chain form of matriptase, and (b) screening the hybridomas to identify hybridomas that produce antibodies that have little or no affinity for the single-chain form of matriptase. The application demonstrates that a screen of about 80 hybridomas that produce monoclonal antibodies that bind to the two-chain form of human matriptase resulted in selection of two hybridomas (M69 and M123) that produce antibodies that are capable of binding specifically to the antigenic two-chain form of matriptase, and do not bind to the single-chain form of matriptase (*see* Example 5, pages 89-91).

The claims that stand rejected and are on appeal are directed to such antibodies that recognize and bind specifically to the two-chain form of matriptase but not the single-chain form of matriptase. In particular, independent claim 16 of the present application is directed to "[a]n isolated antibody or immunologically reactive fragment thereof which selectively binds with greater affinity to a two-chain (active) form of matriptase of a human than to a single-chain (zymogen) form of matriptase of said human." Claims 18 and 34-36 depend from claim 16. Claim 36 is directed to "[t]he antibody or immunologically reactive fragment thereof of claim 16, which binds to the two-chain (active) form of a matriptase protein that is present in a complex comprising HAI-1 or a fragment thereof."

III. GROUNDS OF REJECTION TO BE REVIEWED

In the final official action of August 10, 2005, the examiner identified the following three grounds of rejection under 35 U.S.C. §112, first paragraph, for lack of written description, two of which apply to claims 16, 18, and 34-36, and one of which applies only to claim 36.

1. First ground of rejection that applies to claims 16, 18, and 34-36

Whether description of the primary structures (amino acid sequences), the activating cleavage site, and respective functional activities of the single-chain and two-chain forms of matriptase, and description of two working examples of antibodies that bind with high affinity to different structural features on the antigenic two-chain (active) form of matriptase and have negligible affinity for the single-chain (zymogen) form of matriptase satisfies the written description requirement of 35 U.S.C. §112, first paragraph, for claims directed to the genus of antibodies that bind "with greater affinity to a two-chain (active) form of matriptase of a human than to a single-chain (zymogen) form of matriptase of said human."

2. Second ground of rejection that applies to claims 16, 18, and 34-36

Whether submission of a declaration that hybridomas that produce antibodies M123 and M69 have been deposited under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the public availability of the deposited material will be irrevocably removed upon the granting of a patent, pursuant to 37 C.F.R. § 1.808, and amendment of the

specification to provide the information about the deposited material and the depository, pursuant to 37 C.F.R. § 1.809(d), establishes that the application provides one of skill in the art with a reproducible means for producing the M123 and M69 antibodies for use in identifying the class of antibodies to which the rejected claims are directed.

3. Ground of rejection that applies only to claim 36

Whether description in the specification of the two-chain (active) form of a matriptase protein in a complex with the Kunitz-type serine inhibitor HAI-1 and the disclosure of two examples of different antibodies that bind with high affinity to the antigenic two-chain form of matriptase in a complex with HAI-1 and have little or no affinity for the single-chain form of matriptase satisfies the written description requirement of 35 U.S.C. §112, first paragraph, for an antibody or immunologically reactive fragment thereof that binds with higher affinity to the two-chain (active) form of matriptase in a complex with any Kunitz-type serine inhibitor than to the single-chain form of matriptase.

IV. ARGUMENT

1. First ground of rejection that applies to claims 16, 18, and 34-36

In the final official action, the examiner alleges that rejected claims 16, 18, and 34-36 are directed to a genus of antibodies for which the description in the specification is not sufficient to satisfy the written description requirement of 35 U.S.C. §112, first paragraph. The examiner acknowledges that the specification describes a reproducible method for obtaining the claimed antibodies, and identifies two working examples of the claimed antibodies, antibodies M123 and M69, that bind with high affinity and specificity to the two-chain (active) form of matriptase of a human, and have little or no affinity for the single-chain (zymogen) form of matriptase of said human. However, the examiner argues that the description of the claimed antibodies in the specification fails to support the entire scope of the claimed antibody genus. Specifically, the examiner considers the description of the claimed antibodies to be insufficient because it does not provide "any means of determining what epitope[s] these antibodies target so as to allow those in the art (to) identify any particular structure that may be targeted which structure would correspond to an epitope present in the two-chain but not in the zymogen form of matriptase."

See page 7 of the official action. In the advisory action dated November 30, 2005, the examiner further stated that since the disclosure of two different examples of the claimed antibodies in the specification "provides no information as to the identification of other antibodies within the claimed genus, other than antibodies that bind to the specific epitopes targeted by these two specific antibodies, their disclosure fails to provide adequate support for the claimed genus." *See* page 2 of the advisory action.

The applicants' arguments in response to this ground of rejection are argued separately for (a) claims 16, 34, and 35, (b) claim 18, and (c) claim 36.

Claim 16 is directed to an isolated antibody or immunologically reactive fragment thereof which selectively binds with greater affinity to a two-chain (active) form of matriptase of a human than to a single-chain (zymogen) form of matriptase of said human. Claims 18 and 34-36 are dependent on claim 16.

Claim 18 specifies that the antibody of the claimed invention is a monoclonal antibody, whereas claims 16 and 34-36 do not identify the claimed antibody or fragment thereof as being either monoclonal or polyclonal, and encompass antibodies of either type.

Claim 36 specifies that the antibody of the claimed invention binds to the two-chain (active) form of a matriptase protein that is present in a complex with HAI-1, whereas claims 16, 18, 34, and 35 do not specify whether the claimed antibodies bind to the two-chain (active) form of a matriptase protein that is present in a complex with HAI-1, or to the uncomplexed two-chain (active) form of a matriptase. Unlike claim 36, claims 16, 18, 34, and 35 encompass antibodies that bind to sites on the uncomplexed two-chain (active) form of human matriptase that are sterically inaccessible to antibodies when the two-chain form of matriptase is present in a complex with HAI-1.

Argument with respect to the rejection of claims 16, 34, and 35

The applicants submit that the application describes the antibodies or fragments thereof to which claims 16, 34, and 35 are directed in a manner that satisfies the requirement for written description under 35 U.S.C. §112, first paragraph, for the claimed antibodies.

As discussed above, the examiner alleges that the specification does not satisfy the requirement for written description under 35 U.S.C. §112, first paragraph, for claims 16, 34, and 35, because it does not provide a means for determining the epitope[s] that are targeted by the claimed antibodies so as to allow those in the art to identify any particular structure that corresponds to an epitope present in the two-chain (active) form but not in the zymogen form of matriptase. *See* page 7 of the official action.

The amount and type of information required to satisfy the requirement for written description for a claimed invention under 35 U.S.C. §112, first paragraph, is dependent on the nature of the invention. *See* In re Smyth, 178 U.S.P.Q. 279 at 284 (CCPA 1973). With respect to claims directed to antibodies, it is established that the requirement for written description under 35 U.S.C. §112, first paragraph, for claims directed to antibodies that bind to a well-characterized antigenic protein can be satisfied solely by description of the antigenic protein with reference to such distinguishing parameters as the molecular weight and/or the amino acid sequence of the antigenic protein.

> "In its Guidelines [regarding the requirement for written description under 35 U.S.C. §112, first paragraph], the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics... *i.e.,* complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure,* or some combination of such characteristics." *Guidelines,* 66 Fed. Reg. at 1106 (emphasis added). For example, the PTO would find compliance with 112, 1, for a claim to an isolated antibody capable of binding to antigen X, notwithstanding the functional definition of the antibody, in light of the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature. Synopsis of Application of Written Description Guidelines, at 60, *available at* http://www.uspto.gov/web/patents/guides.htm (*Application of Guidelines*)."

See Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964 (Fed. Cir., 2002). Moreover, the PTO routinely issues patents with claims directed to antibodies that bind specifically to an antigenic protein that is disclosed and characterized by the corresponding application

specifications, without requiring identification of the specific epitopes on the protein that are bound by the claimed antibodies, or without even requiring a demonstration that the claimed antibodies have been produced. The PTO's Written Description Guidelines, the examining practice of the PTO, and the Court of Appeals of the Federal Circuit, have recognized that in view of the well defined structural characteristics of antibodies, the functional characteristics of antibody binding, and the developed and mature state of antibody technology, an application that describes and fully characterizes an antigenic protein in structural and chemical terms satisfies the written description requirement of 35 U.S.C. §112, first paragraph, with respect to claims directed to antibodies that bind specifically to the characterized antigenic protein.

In the present application, the applicants have disclosed and characterized an antigenic protein, the active, two-chain form of human matriptase, *e.g.*, in terms of its amino acid sequence (SEQ ID NO: 4), the location of the site of cleavage that activates the enzyme (*e.g.*, *see* page 78 and Figs. 9 and 10), and residues of the substrate-binding site (*see* pages 66-67). The application also demonstrates that the two-chain form of human matriptase is structurally and functionally distinct from the single chain form of matriptase, as evidenced by the disclosure that HAI-1 binds to and forms a complex with the two-chain form of matriptase, but does not bind to the single-chain form of human matriptase inability of the single-chain form of matriptase to form a complex with HAI-1 (*e.g.*, *see* page 78), and that the single-chain form of matriptase does not possess proteolytic activity (*e.g.*, *see* pages 66-67 and Fig. 14). Antibody fragments such as those of claim 34 are described in the application, *e.g.*, on page 21, lines 15-24. The nucleotide sequence of SEQ ID NO: 4 encoding the polypeptide of single-chain form of matriptase specified in claim 35 is described, *e.g.*, in Figure 9, and cleavage of said single-chain form of matriptase to produce the two-chain form of matriptase as specified in claim 35 is described in the application, *e.g.*, on pages 78-79. As described by the specification, an object of the invention is "to provide an antibody or antibodies which recognizes and binds to SEQ ID NO:3 or a fragment thereof, SEQ ID NO:4 or a fragment thereof, to a single-chain (zymogen) form of matriptase or to a two-chain (active) form of matriptase," and describes preferred antibodies as being "monoclonal antibodies or fragments thereof as well as chimeric, humanized or human antibodies" (*see* page 14, lines 20-25). In Example 5 of the application, the applicants describe reliable screening and assay procedures by which one of skill in the art can identify hybridoma

clones that produce the claimed antibodies that bind specifically to the antigenic two-chain form of human matriptase and have little or no binding affinity for the single-chain form of matriptase. As described in the working example, the two-chain form of human matriptase present in a complex with HAI-1 was used as immunogen to produce approximately 80 hybridoma clones that produce antibodies that bind both the two-chain form of human matriptase complexed with HAI-1, and to the uncomplexed two-chain form of human matriptase. The approximately 80 hybridoma clones were then screened as described, and two disclosed hybridoma clones, M69 and M123, were identified that produce antibodies of the claimed invention that bind with high affinity and specificity to the antigenic two-chain (active) form of human matriptase and do not bind to the single-chain (zymogen) form of the protein. Differences in binding affinity of M69 and M123 for the non-boiled and boiled 95 kDa complex of HAI-1 and matriptase indicate that the two antibodies bind to different structural features on the antigenic two-chain form of matriptase. *See* Example 5, pages 89-91. The application thus both describes and discloses two working examples of the claimed antibodies, and one of skill in the art would reasonably expect to obtain additional examples of the claimed antibodies by routine screening using a screening method such as that which is described in the specification.

Moreover, as the application teaches that HAI-1 binds to and forms a complex with the two-chain form of human matriptase, but does not bind to the single-chain form of human matriptase, it would be clear to one of skill in the art that HAI-1 binds to structural features of the two-chain (active) form of human matriptase that are altered or absent on the single-chain (zymogen) form of matriptase, and which are exposed as additional antibody binding sites on the surface of the uncomplexed two-chain form of human matriptase. One of skill in the art therefore would reasonably expect that the uncomplexed two-chain form of human matriptase can be used as immunogen in the disclosed method for producing the claimed antibodies for production of even higher yields of the claimed antibodies than the 1:40 ratio of antibodies specific for the two-chain (active) form of matriptase per hybridoma screened that was obtained in the disclosed example.

Furthermore, the application teaches that one of skill in the art can use known methods to prepare monoclonal or polyclonal antibodies that bind specifically to polypeptide fragments of the disclosed matriptase amino acid sequence (*see* pages 36-37). While the application describes

a working example of the method wherein the complete two-chain form of human matriptase is used as immunogen for preparing the claimed antibodies, one of skill in the art would readily be able to use well known and routine immunological methods for preparing antibodies that bind peptide fragments to identify specific structures (epitopes) bound by antibodies prepared by the exemplified method in which the entire two-chain form of matriptase is used as immunogen, *e.g.*, by competition screening.

The representative number of species within a genus of a claimed invention that must be disclosed to satisfy the requirement for written description under 35 U.S.C. §112, first paragraph, depends on the nature and predictability of the field of the invention (*see* Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). As discussed above, decisions by the Court of Appeals of the Federal Circuit and PTO practice evidence a recognition that in view of the well defined structural characteristics of antibodies, the functional characteristics of antibody binding, and the developed and mature state of antibody technology, an application that describes and fully characterizes an antigenic protein in structural and chemical terms satisfies the written description requirement of 35 U.S.C. §112, first paragraph, with respect to claims directed to antibodies that bind specifically to the characterized antigenic protein, even if the claimed antibodies have not been produced.

In accordance with the above, the applicants submit that the disclosure in the specification of two different antibodies, M69 and M123, that bind with high affinity to the two-chain form of human matriptase and have little or no affinity for the single-chain form of matriptase provides a representative number of species within the genus of the claimed invention in satisfaction of the requirement for written description under 35 U.S.C. §112, first paragraph. As pointed out above, the specification describes and characterizes the two-chain form of human matriptase in structural and chemical terms, *e.g.*, in terms of its amino acid sequence (SEQ ID NO: 4), the site of cleavage that activates the enzyme (*e.g.*, *see* page 78 and Figs. 9 and 10), and the amino acids that form the substrate-binding site (*see* pages 66-67) and catalytic site (*see* page 64). Since the application characterizes the antigenic two-chain form of human matriptase in chemical and structural terms that permit it to be clearly distinguished from the single-chain form of matriptase and from other proteins, and further describes two representative working examples of antibodies that bind to different structural features of the two-chain form of human

matriptase and do not bind to the single-chain form of matriptase, one of skill in the art would reasonably have considered the applicants to have been in possession of the claimed invention at the time of filing. Accordingly, the applicants respectfully submit that the application satisfies the written description requirement of 35 U.S.C. §112, first paragraph, for claims 16, 34, and 35.

Argument with respect to the rejection of claim 18

The applicants respectfully submit that the application describes the antibodies to which claim 18 is directed in a manner that satisfies the requirement for written description under 35 U.S.C. §112, first paragraph, for the claimed antibodies.

The examiner alleges that the specification does not satisfy the requirement for written description under 35 U.S.C. §112, first paragraph, for claim 18, because it does not provide a means for determining the epitope[s] that are targeted by the claimed antibodies so as to allow those in the art to identify any particular structure that corresponds to an epitope present in the two-chain (active) form but not in the zymogen form of matriptase, as discussed above for claims 16, 34, and 35. *See* page 7 of the official action.

The arguments presented above in support of the patentability of claims 16, 34, and 35 are also applicable with respect to claim 18. It is therefore requested that the arguments stated above with respect to the rejection of claims 16, 34, and 35, also be applied and considered fully with respect to the rejection of claim 18 for alleged non-compliance with the written description requirement of 35 U.S.C. §112, first paragraph.

Claim 18 is directed to an isolated antibody or immunologically reactive fragment thereof which selectively binds with greater affinity to a two-chain (active) form of matriptase of a human than to a single-chain (zymogen) form of matriptase of said human as set forth in claim 16, wherein the antibody is a monoclonal antibody. As discussed above, the application describes a method for preparing monoclonal antibodies that selectively bind with high affinity to a two-chain (active) form of human matriptase, and have little or no affinity for the single-chain (zymogen) form of human matriptase. The application also describes two examples of the claimed monoclonal antibodies, M69 and M123, that bind with high affinity to different structural features of the two-chain (active) form of matriptase and have little or no affinity for the single-chain (zymogen) form of human matriptase (*see* Example 5).

As discussed above, decisions of the Court of Appeals of the Federal Circuit and the practice of the USPTO evidence the recognition that an application that describes and fully characterizes an antigenic protein in structural and chemical terms satisfies the written description requirement of 35 U.S.C. §112, first paragraph, with respect to claims directed to antibodies that bind specifically to the characterized antigenic protein, even if the claimed antibodies have not been produced. Accordingly, the applicants submit that the description of methods by which the claimed antibodies can be prepared, and the disclosure in the specification of two different monoclonal antibodies, M69 and M123, that bind with high affinity to the two-chain form of human matriptase and have little or no affinity for the single-chain form of matriptase, satisfy the requirement for written description under 35 U.S.C. §112, first paragraph, of the genus of monoclonal antibody to which claim 18 is directed.

Argument with respect to the rejection of claim 36

The applicants respectfully submit that the application describes the antibodies to which claim 36 is directed in a manner that satisfies the requirement for written description under 35 U.S.C. §112, first paragraph, for the claimed antibodies.

Claim 36 is directed to an isolated antibody or immunologically reactive fragment thereof which selectively binds with greater affinity to a two-chain (active) form of matriptase of a human than to a single-chain (zymogen) form of matriptase of said human as set forth in claim 16, wherein the antibody or fragment thereof binds to the two-chain (active) form of a matriptase protein that is present in a complex comprising HAI-1.

In the final official action, the examiner rejects claim 36 under 35 U.S.C. §112, first paragraph, for alleged lack of written description, for the reasons described above for claims 16, 18, 34, and 35, and further rejects claim 36 because antibody M123 allegedly binds to the two-chain (active) form of human matriptase and performs the function of the inhibitor HAI-1, but the application is not considered to adequately describe antibodies such as antibody M123 that perform the function of HAI-1.

The applicants respectfully submit that the examiner has incorrectly characterized the activity and function of antibody M123 as described by the specification. The specification does

not describe antibody M123 as being capable of performing the function of the inhibitor protein HAI-1. As described in Example 5 of the specification, antibodies M69 and M123 were both obtained by screening hybridomas that were generated using the 95 kDa complex of HAI-1 and the two-chain form of human matriptase as immunogen. Therefore, both the M69 and M123 antibodies are described in the specification as working examples of antibodies that bind with high affinity to the two-chain (active) form of human matriptase protein that is present in a complex comprising HAI-1, and have little or no affinity for the single-chain (zymogen) form of human matriptase, as set forth in claim 36.

All of the arguments presented above in support of the patentability of claims 16, 34, and 35 are also applicable with respect to claim 36, with the exception that the antibodies of claim 36 do not include antibodies that bind to structural features of the uncomplexed two-chain (active) form of human matriptase that are unavailable as antigen-binding sites on the two-chain (active) form of human matriptase that is present in a complex with HAI-1. It is therefore requested that the arguments stated above with respect to the rejection of claims 16, 34, and 35, with the exception noted above, also be applied and considered fully with respect to the rejection of claim 36 for alleged non-compliance with the written description requirement of 35 U.S.C. §112, first paragraph. Accordingly, the applicants submit that the description of methods by which the claimed antibodies can be prepared, and the disclosure in the specification of two different antibodies, M69 and M123, that bind with high affinity to the two-chain form of human matriptase in complex with HAI-1 that have little or no affinity for the single-chain form of matriptase, satisfy the requirement for written description under 35 U.S.C. §112, first paragraph, of the genus of antibody to which claim 36 is directed.

2. Second ground of rejection that applies to claims 16, 18, and 34-36

The applicants submit that the application describes the antibodies or fragments thereof to which claims 16, 18, and 34-36 are directed in a manner that satisfies the requirement for written description under 35 U.S.C. §112, first paragraph, for the claimed antibodies.

In the final official action, the examiner further rejected claims 16, 18, and 34-36 under 35 U.S.C. §112, first paragraph, because the application was not considered to provide one of skill in the art with a reproducible means for producing the M123 and M69 antibodies for use in

identifying the class of antibodies to which the rejected claims are directed. A declaration was submitted with the response to the final official action filed on November 8, 2005, declaring that hybridomas that produce antibodies M123 and M69 have been deposited under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the public availability of the deposited material will be irrevocably removed upon the granting of a patent, pursuant to 37 C.F.R. § 1.808, and the response amended the specification to provide the accession number, date, and description of the deposits, and the name and address of the depository, pursuant to 37 C.F.R. § 1.809(d). The applicants submit that the declaration and amendment filed on November 8, 2005, overcome the stated ground for rejection of claims 16, 18, and 34-36 under 35 U.S.C. §112, first paragraph, for lack of written description with respect to provision of evidence of a reproducible means for obtaining antibodies M123 and M69.

3. **Ground of rejection that applies only to claim 36**

The applicants submit that the application describes the antibodies or fragments thereof to which claims 36 are directed in a manner that satisfies the requirement for written description under 35 U.S.C. §112, first paragraph, for the claimed antibodies.

In the final official action, the examiner further rejected claim 36 under 35 U.S.C. §112, first paragraph, because the application was not considered to provide adequate description of a two-chain form of a matriptase protein in a complex with any Kunitz-type inhibitor other than HAI-1. *See* page 9 of the official action. In the response to the final official action filed on November 8, 2005, claim 36 was amended to specify that the Kunitz-type inhibitor present in the complex with the two-chain (active) form of human matriptase protein is HAI-1. The applicants respectfully submit that amendment of claim 36 to identify HAI-1 as the Kunitz-type inhibitor in the complex overcomes the stated ground for rejection of claim 36 under 35 U.S.C. §112, first paragraph, for lack of written description with respect to the type of Kunitz-type inhibitor in the complex.

V. CONCLUSION

For at least the reasons discussed above, it is respectfully submitted that the description of the claimed invention provided by the application satisfies the requirement for written description under 35 U.S.C. §112, first paragraph, for rejected claims 16, 18, and 34-36.

For the above reasons, Appellants respectfully request this Honorable Board to reverse the rejection of the claims.

Respectfully submitted,

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VI. APPENDIX – CLAIMS ON APPEAL

16. An isolated antibody or immunologically reactive fragment thereof which selectively binds with greater affinity to a two-chain (active) form of matriptase of a human than to a single-chain (zymogen) form of matriptase of said human.

18. The antibody or immunologically reactive fragment thereof of claim 16, wherein the antibody is a monoclonal antibody.

34. The antibody or immunologically reactive fragment thereof of claim 16, wherein the immunologically reactive fragment is selected from the group consisting of scFv, Fab, Fab', and $F(ab')_2$.

35. The antibody or immunologically reactive fragment thereof of claim 16, wherein said single-chain form of matriptase comprises a polypeptide encoded by the nucleotide sequence of SEQ ID NO: 4, and the two-chain form of matriptase is produced by cleavage of said single-chain form of matriptase.

36. The antibody or immunologically reactive fragment thereof of claim 16, which binds to the two-chain (active) form of a matriptase protein that is present in a complex comprising Hepatocyte growth factor activator inhibitor-1 (HAI-1) or a fragment thereof.

VII. APPENDIX – RELATED PROCEEDINGS

NONE